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Claim 1 (three-times amended):

An implantable bone paste composition comprising gelatin as a carrier for one or more substantially bioabsorbable, osteogenic components for use in a recipient in need thereof,

wherein said one or more osteogenic components are selected from the group consisting of: (i) demineralized bone matrix (DBM); (ii) bone morphogenetic protein, TGF-beta, PDGF, or mixtures thereof, natural or recombinant; and (iii) mixtures of (i) and (ii).

Point of Contact:
Mary Hale
Technical Info. Specialist
CM1 12D16 Tel: 308-4258

Claim 33 (amended):

A method for making an implantable graft which comprises preparing a composition comprising a thermally cross-linkable gelatin carrier and suspending therein [a] one or more substantially bioabsorbable, osteogenic [component] components; wherein said one or more osteogenic components are selected from the group consisting of: (i) demineralized bone matrix (DBM); (ii) bone morphogenetic protein, TGF-beta, PDGF, or mixtures thereof, natural or recombinant; and (iii) mixtures of (i) and (ii).

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PTO-1590 (9-90)

Burston
816079

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=> fil medl,caplus,biosis,embase,wpids;s implant? bone paste

COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                      ENTRY      SESSION
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L1 0 FILE MEDLINE
L2 2 FILE CAPLUS
L3 0 FILE BIOSIS
L4 0 FILE EMBASE
L5 2 FILE WPIDS

TOTAL FOR ALL FILES
L6 4 IMPLANT? BONE PASTE

1997

=> dup rem l6

PROCESSING COMPLETED FOR L6
L7 2 DUP REM L6 (2 DUPLICATES REMOVED)

=> d 1-2 cbib abs;s gelatin and (demineral? bone matrix or dbm or bone morphogenetic protein or tgf beta or pdgf)

L7 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2000 ACS DUPLICATE 1
1999:495201 Document No. 131:134686 Bone pastes comprising osteogenic compounds in a sterilized gelatin matrix. Wironen, John F.; Felton, Phillip A.; Jaw, Rebecca (Regeneration Technologies, Inc., USA; University of Florida Tissue Bank, Inc.). PCT Int. Appl. WO 9938543 A2 19990805, 37 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US1677 19990127. PRIORITY: US 1998-14519 19980128; US 1998-154400 19980916.

AB A thermally sterilized bone paste useful in the orthopedic arts, for example in the repair of non-union fractures, periodontal ridge augmentation, craniofacial surgery, implant fixation, impaction grafting, or any other procedure in which generation of new bone is deemed necessary, is provided by a compn. comprising a substantially bioabsorbable osteogenic compd. in a matrix of 11-19 %, preferably 15-19 % of thermally sterilized gelatin. In various embodiments, the osteogenic compd. is selected from (1) demineralized bone matrix (DBM); (2) bioactive glass ceramic, Bioglass, bioactive ceramic, calcium phosphate ceramic, hydroxyapatite, hydroxyapatite carbonate, corraline hydroxyapatite, calcined bone, tricalcium phosphate, or like material; (3) bone marrow exts., vascular proliferation or regeneration growth factors, bone morphogenetic protein, TGF-.beta., PDGF, or mixts. thereof, natural or recombinant; and (4) mixts. of (1)-(3). The thermally sterilized gelatins may be a com. available grade of gelatins which is both thermally and irradiatively sterilized.

L7 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2000 ACS DUPLICATE 2
1998:624020 Document No. 129:250241 Bone paste comprising a bioabsorbable osteogenic compound in a gelatin matrix. Wironen, John F.; Grooms, Jamie M. (University of Florida Tissue Bank, Inc., USA; University of Florida Research Foundation, Inc.). PCT Int. Appl. WO 9840113 A1 19980917, 39 pp.
DESIGNATED STATES: W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, GW,

HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US4904 19980312. PRIORITY: US 1997-816079 19970313.

AB A bone paste useful in the orthopedic arts, for example in the repair of non-union fractures, periodontal ridge augmentation, craniofacial surgery, implant fixation, impaction grafting, or any other procedure in which generation of new bone is deemed necessary, is provided by a compn. comprising a substantially bioabsorbable osteogenic compd. in a gelatin matrix. In various embodiments, the osteogenic compd. is selected from (1) demineralized bone matrix (DBM); (2) bioactive glass ceramic, Bioglass, bioactive ceramic, calcium phosphate ceramic, hydroxyapatite, hydroxyapatite carbonate, corraline hydroxyapatite, calcined bone, tricalcium phosphate, or like material; (3) bone morphogenetic protein, TGF-.beta., PDGF, or mixts. thereof, natural or recombinant; and (4) mixts. of (1)-(3). The bone paste contains dry demineralized bone 0-40, lyophilized thermally crosslinkable gelatin 20-45, Bioglass 0-40%, and bone morphogenic protein 0.001 mg/mL. The bone paste was osteoinductive when implanted in rats.

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L8          87 FILE MEDLINE
L9         113 FILE CAPLUS
L10         58 FILE BIOSIS
L11         75 FILE EMBASE
L12         19 FILE WPIDS

TOTAL FOR ALL FILES
L13        352 GELATIN AND (DEMINERAL? BONE MATRIX OR DBM OR BONE
MORPHOGENETIC
                PROTEIN OR TGF BETA OR PDGF)

=> s l13 and (graft or bone paste)

L14          9 FILE MEDLINE
L15          8 FILE CAPLUS
L16          4 FILE BIOSIS
L17          9 FILE EMBASE
L18          2 FILE WPIDS

TOTAL FOR ALL FILES
L19         32 L13 AND (GRAFT OR BONE PASTE)

=> s l19 not l6\

L20          9 FILE MEDLINE
L21          8 FILE CAPLUS
L22          4 FILE BIOSIS
L23          9 FILE EMBASE
L24          2 FILE WPIDS

TOTAL FOR ALL FILES
L25         32 L19 NOT L6\

=> s l19 not l6

L26          9 FILE MEDLINE
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L27 6 FILE CAPLUS
L28 4 FILE BIOSIS
L29 9 FILE EMBASE
L30 0 FILE WPIDS

TOTAL FOR ALL FILES
L31 28 L19 NOT L6

=> dup rem l31

PROCESSING COMPLETED FOR L31
L32 18 DUP REM L31 (10 DUPLICATES REMOVED)

=> d 1-18 cbib abs;s l13 and implant? and osteogen? and bioabsorb?

L32 ANSWER 1 OF 18 CAPLUS COPYRIGHT 2000 ACS
2000:123795 Rabbits' radius segmental bone defect repaired with compound materials of BMG particles impregnated with bone cement and bBMP. Hu, Yunsheng; Fan, Qingyu; Yang, Lianjia; Zhou, Yong; Jiang, Weizhong; Qiu, Xiuchun; Wen, Yanhua (Orthopedics Oncology Institute of Chinese PLA, Tangdu Hospital, Fourth Military Medical University, Xi'an, 710038, Peop. Rep. China). Disi Junyi Daxue Xuebao, 20(12), 1071-1074 (Chinese) 1999. CODEN: DJDXEG. ISSN: 1000-2790. Publisher: Disi Junyi Daxue Xuebao Bianjibu.
AB The osteogenesis and the form of new bone formation in repairing bone defect using the compd. materials of the allogenic bone matrix **gelatin** (BMG) particles, impregnated with polymethyl- methacrylate bone cement and bovine **bone morphogenetic proteins** were studied. The compd. materials and autologous bone were implanted in New Zealand rabbit's radius bone defects resp. The samples were obsd. with gross, X-ray, single photo emission computed tomog., histomorphol. and scanning electronic microscope at different periods after operation to study the form of new bone formation and osteogenesis of the compd. materials in contrast to autologous bone. There was no significant deference in the healing rate between the compd. materials and autologous bone. The compd. material **graft** was similar to the fresh autologous bone **graft** in the healing process and the form of new bone formation. Allogenic BMG particles impregnated with bone cement act as a good bBMP slow releasing carriers and the compd. materials possess a superior bone induction. The results of rabbits' radius bone defect repaired with the compd. materials are satisfactory.

L32 ANSWER 2 OF 18 MEDLINE DUPLICATE 1
1999284027 Document Number: 99284027. Potential of porous poly-D,L-lactide-co-glycolide particles as a carrier for recombinant human **bone morphogenetic protein**-2 during osteoinduction in vivo. Boyan B D; Lohmann C H; Somers A; Niederauer G G; Wozney J M; Dean D D; Carnes D L Jr; Schwartz Z. (Department of Orthopaedics, University of Texas Health Science Center, San Antonio 78284-7774, USA.. boyanb@uthscsa.edu) . JOURNAL OF BIOMEDICAL MATERIALS RESEARCH, (1999 Jul) 46 (1) 51-9. Journal code: HJJ. ISSN: 0021-9304. Pub. country: United States. Language: English.
AB Several different biodegradable bone **graft** materials are in clinical or preclinical use for the repair of bone defects in orthopedics, maxillofacial surgery, and periodontics. This study tested the hypothesis that poly-D,L-lactide-co-glycolide copolymer (PLG) can be used as an effective carrier of recombinant human **bone**

morphogenetic protein-2 (rhBMP-2) and that the composite has osteoinductive ability. Porous PLG rods were shredded to a particle size ranging from 250 to 850 microm. Active and inactive demineralized freeze-dried bone allografts (DFDBA) with a comparable particle size were used as positive and negative controls, respectively. PLG particles were treated with vehicle or with 5 or 20 microg rhBMP-2. DFDBA and PLG particles were placed in **gelatin** capsules, mixed with vehicle or rhBMP-2, and implanted at intramuscular sites in male Nu/Nu (nude) mice. Each mouse underwent bilateral implantation with implants of the same formulation, resulting in five groups of four mice per group: active DFDBA, inactive DFDBA, PLG, PLG + 5 microg rhBMP-2, and PLG + 20 microg rhBMP-2. After 56 days, the implants were recovered and processed for histology. Bone induction was assessed by use of a semiquantitative scoring system based on the amount of new bone formed in representative histological sections. Histomorphometry was also used to measure the area of new bone formed and the area of residual implant material. The results showed that active DFDBA induced the formation of ossicles containing new bone with bone marrowlike tissue, whereas inactive DFDBA or PLG particles alone did not induce new bone. The addition of rhBMP-2 to PLG particles resulted in new bone formation that had a greater bone induction score than active DFDBA. Moreover, the histomorphometric analysis showed that the addition of rhBMP-2 to PLG particles induced the formation of a greater area of new bone and bone marrowlike tissue than active DFDBA. The resorption of the PLG particles was markedly increased with the addition of rhBMP-2, suggesting that rhBMP-2 may attract and regulate resorptive cells at the implantation site. The results of the present study indicate that PLG copolymers are good carriers for BMP and promote the induction of new bone formation. Further, the PLG copolymers with rhBMP-2 had a greater effect in inducing new bone formation and resorbing the implanted material than active DFDBA alone.

L32 ANSWER 3 OF 18 BIOSIS COPYRIGHT 2000 BIOSIS

1999:104821 Document No.: PREV199900104821. The correlation between immune rejection and osteoinduction of allogeneic bone grafting. Sun, Lei; Hu, Yunyu (1); Ning, Zhijie (1); Liang, Zhe. (1) Orthop. Cent. CPLA, 88th Hosp., Tai'an 271000 China. Chinese Medical Journal (English Edition), (Sept., 1998) Vol. 111, No. 9, pp. 818-822. ISSN: 0366-6999. Language: English.

AB Objective. To evaluate the relationship between the immune rejection and the osteoinductive potential of bone allograft. Methods. Allogeneic and syngeneic fresh bone, autolyzed antigen-extracted bone, bone matrix **gelatin** and **demineralized bone matrix** were implanted into the muscle of mice, and immunological tests, histological observation and alkaline phosphatase assay were performed. Results. Three and 6 weeks after implantation, all kinds of allogeneic implants activated immune rejection, among them, fresh bone induced the most vigorous immune rejection and bone matrix **gelatin** caused the weakest response. Allogeneic autolyzed antigen-extracted bone, bone matrix **gelatin** and **demineralized bone matrix** inhibited proliferation of the lymphocytes in vitro and bone matrix **gelatin** had the most powerful inhibiting effect. Both allogeneic and syngeneic autolyzed antigen-extracted bone, bone matrix **gelatin**, and **demineralized bone matrix** induced heterotopic osteogenesis in vivo and bone matrix **gelatin** had the best osteoinductive capacity. Conclusion. There is a negative correlation between immune rejection to bone allograft and osteoinductive capacity of the **graft**.

L32 ANSWER 4 OF 18 MEDLINE DUPLICATE 2
1998255075 Document Number: 98255075. Repair of ulnar segmental defect by recombinant human **bone morphogenetic protein** -2 in dogs. Itoh T; Mochizuki M; Nishimura R; Matsunaga S; Kadosawa T; Kokubo S; Yokota S; Sasaki N. (Laboratory of Veterinary Surgery, Graduate School of Agriculture and Life Science, University of Tokyo, Japan.) JOURNAL OF VETERINARY MEDICAL SCIENCE, (1998 Apr) 60 (4) 451-8. Journal code: A27. ISSN: 0916-7250. Pub. country: Japan. Language: English.

AB The efficacy of recombinant human **bone morphogenetic protein**-2 (rhBMP-2) combined with poly D, L lactic-co-glycolic acid (PLGA)/**gelatin** sponge complex (PGS) as a carrier on the repair of segmental long-bone defects was evaluated using an ulnar model in dogs. The defect was 2 cm in length and was fixed with bone plating. After implantation of PGS with or without rhBMP-2, the repair process of the defect was evaluated by serial radiography until 16 postoperative weeks. All defects treated with 160 micrograms or 640 micrograms of rhBMP-2/PGS revealed bone union radiographically by 12 postoperative weeks, whereas all defects treated with PGS alone revealed no radiographic evidence of healing throughout the experimental period. In defects treated with 40 micrograms of rhBMP-2/PGS, new bone appeared partially at the defects but did not accomplish union. Bone mineral contents at the defect sites after harvest at 16 weeks postoperatively were significantly ($p < 0.05$) higher in those treated with 160 micrograms or 640 micrograms of rhBMP-2 than in those treated with 40 micrograms of rhBMP-2 or PGS alone. Histologically, defects radiographically diagnosed as having achieved union showed the appearance of cortical bone and bone marrow cells. These findings suggest the use of rhBMP-2/PGS as a potential bone **graft** substitute in reconstructive surgery in dogs.

L32 ANSWER 5 OF 18 MEDLINE
1998086951 Document Number: 98086951. Bone formation and osseointegration stimulated by rhBMP-2 following subantral augmentation procedures in nonhuman primates. Hanisch O; Tatakis D N; Rohrer M D; Wohrle P S; Wozney J M; Wikesjo U M. (Department of Prosthodontics, University of Aachen, Germany.) INTERNATIONAL JOURNAL OF ORAL AND MAXILLOFACIAL IMPLANTS, (1997 Nov-Dec) 12 (6) 785-92. Journal code: GJR. ISSN: 0882-2786. Pub. country: United States. Language: English.

AB The purpose of this study was to evaluate bone formation and osseointegration using titanium dental implants in the subantral space following surgical implantation of recombinant human **bone morphogenetic protein**-2 (rhBMP-2). In each of four cynomolgus monkeys, one subantral site was treated with rhBMP-2 (0.19 mg per implant) in an absorbable collagen sponge (ACS). The contralateral site was treated with vehicle in ACS (control). Three months later, two screw-type titanium dental implants were placed into each augmented sinus, and one additional implant was placed immediately anterior to the sinus. Thus, each animal had three experimental sites: rhBMP-2, control, and nonsinus. Animals were sacrificed after an additional 3 months, and block sections were harvested and prepared for histometric analysis. Analysis of variance and t tests were used to evaluate differences between experimental conditions. Mean (+/- SD) vertical bone gain was significantly greater in rhBMP-2 than in control sites (6.0 +/- 0.3 versus 2.6 +/- 0.3 mm; $P < .002$). Bone density in rhBMP-2 sites averaged 14.4 +/-

2.9% versus 13.9 +/- 4.6% and 14.1 +/- 3.6% for control and nonsinus sites, respectively, without significant differences between experimental conditions. Bone-implant contact in rhBMP-2 sites (41.4 +/- 7.7%) was not significantly different from that in control (38.9 +/- 12.4%) and nonsinus sites (46.8 +/- 10.6%). The present study provides evidence for considerable vertical bone gain in the subantral space following surgical implantation of rhBMP-2, thus allowing placement of dental implants. The newly formed bone appears to be of similar quality and to be as suitable for osseointegration as the residual bone in this nonhuman primate model. Thus, surgical implantation of rhBMP-2 appears to have clinical utility and may provide a realistic alternative to autogenous bone **grafts** for subantral augmentation procedures.

L32 ANSWER 6 OF 18 CAPLUS COPYRIGHT 2000 ACS DUPLICATE 3
1998:4824 Document No. 128:106366 Induction of osteogenesis in repairing bone defects of rabbits. Tu, Guanjun; Jin, Yaoqing; Deng, Xiandong; Wang, Taizeng (Dep. Orthopaedics, First Clinical Coll., China Medical Univ., Shenyang, 110001, Peop. Rep. China). Zhongguo Yike Daxue Xuebao, 26(2), 153-155, 158 (Chinese) 1997. CODEN: ZYDXEN. ISSN: 0258-4646. Publisher:
Zhongguo Yike Daxue.
AB The repairing of bone defects was conducted by composite **grafts** of bone matrix **gelatin** (BMG) and autogenous bone marrow (ABM) or **demineralized bone matrix** (DMB) and ABM resp. The process qual. and quant. were obsd. Both of them had the capacity of osteoinduction. BMG was superior to **DBM**. The results suggest that DMG and **DBM** contained **bone morphogenetic protein** (BMP) which had the effect of osteoinduction, whereas ABM was the target cells of BMP.

L32 ANSWER 7 OF 18 CAPLUS COPYRIGHT 2000 ACS
1996:404741 Document No. 125:67853 Osteoplastic **graft**. Yokota, Shoji; Shimokawa, Seitaro; Sonohara, Ritsu; Okada, Akira; Takahashi, Koichiro (Japan). PCT Int. Appl. WO 9610426 A1 19960411, 51 pp. DESIGNATED STATES: W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KE, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TT, UA, US, UZ, VN; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2.
APPLICATION:
WO 1995-JP1970 19950928. PRIORITY: JP 1994-261980 19940930.
AB An osteoplastic **graft** comprises a bone inducer supported on a composite porous body comprising a porous structure of a bioabsorbable hydrophilic material and a surface layer of a bioabsorbable polymeric material. Preferably, the hydrophilic material comprises at least one member selected from the group consisting of **gelatin**, hyaluronic acid and derivs. thereof, collagen and derivs. thereof, chitosan and derivs. thereof, and triethanolammonium alginate, while the polymeric material comprises at least one member selected from the group consisting of polylactic acid, polylactic acid-polyglycolic acid copolymer, and poly[bis(p-carboxyphenoxy)propane] anhydride-sebacic acid copolymer. As the **graft** is excellent in moldability and operability and has an internal structure suitable for in vivo bone neogenesis, bone grafting occurs not only at the periphery of the **graft** but also within the **graft**.

L32 ANSWER 8 OF 18 MEDLINE
1998256545 Document Number: 98256545. Immunological comparison of

differently treated allografts of bone. Sun L; Hu Y; Ning Z. (Department of Orthopedics, 88th Hospital of People's Liberation Army, Tai'an.) CHUNG-HUA WAI KO TSA CHIH [CHINESE JOURNAL OF SURGERY], (1996 Aug) 34 (8) 460-3. Journal code: D86. ISSN: 0529-5815. Pub. country: China. Language:
Chinese.

AB The immunnologic rejection induced by differently treated allografts of bone was compared. Methods Fresh bone (FB), autolyzed antigen-free bone (AAA), bone matrix **gelatin** (BMG), **demineralized bone matrix** (DBM) were implanted into the muscle pouch of mice, then, the immunological tests and alkaline phosphatase assay were conducted. Results Allogeneic FB induced the highest level of serum antibody in the host and stimulated lymphocytes proliferation remarkably in vitro; in contrast, AAA, BMG and **DBM** caused low titer of antibody and inhibited lymphocytes reproduction in vitro. Conclusions. Immunological rejection restrained osteogenesis of the bone implant, whereas the osteoinductive substance of bone suppressed immunological reaction.

L32 ANSWER 9 OF 18 CAPLUS COPYRIGHT 2000 ACS

1997:516024 Document No. 127:204438 A correlative study on the immune rejection and osteoinductive capacity of bone allograft. Sun, Lei; Hu, Yunyu; Liang, Zhe; Lu, Rong; Ning, Zhijie; Wang, Yuqing; Lu, Yulin (Department of Orthopedics, The 88th Hospital of PLA, Tai'an, 271000, Peop. Rep. China). Zhonghua Chuangshang Zazhi, 12(6), 356-359 (Chinese) 1996. CODEN: ZCZAFD. ISSN: 1001-8050. Publisher: Zhonghua Chuangshang Zazhi Bianjibu.

AB The correlation between the immune rejection and the osteoinductive potential of bone allograft was studied. Allogeneic and syngeneic fresh bone (FB), autolyzed antigen-extd. bone (AAA), bone matrix **gelatin** (BMG), and **demineralized bone matrix** (**DBM**) were implanted into the muscle of mice, and immunol. tests, histol. observation and alk. phosphatase (ALP) assay were performed. All allogeneic implants activated immune rejection. Among them, FB induced the most vigorous immune rejection and BMG caused the weakest response. Allogeneic AAA, BMG and **DBM** inhibited proliferation of the lymphocytes in vitro and BMG had the most powerful inhibiting effect. Both allogeneic and syngeneic BMG, **DBM** and AAA induced heterotopic osteogenesis in vivo and BMG had the best osteoinductive capacity. The results suggest that there is neg. correlation between immune rejection to bone allograft and osteoinductive capacity of the **graft**.

L32 ANSWER 10 OF 18 MEDLINE DUPLICATE 4

95221902 Document Number: 95221902. T lymphocytes infiltrating sites of tumor rejection and progression display identical V beta usage but different cytotoxic activities. Kurt R A; Park J A; Panelli M C; Schluter S F; Marchalonis J J; Carolus B; Akporiaye E T. (Department of Microbiology and Immunology, University of Arizona, Arizona Health Sciences Center, Tucson 85724, USA..) JOURNAL OF IMMUNOLOGY, (1995 Apr 15) 154 (8) 3969-74. Journal code: IFB. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Most tumors grow progressively and overwhelm the host. The rare but documented cases of spontaneous regression of primary tumors are indicative of the potential of tumor-bearing hosts to develop a significant antitumor response. Because most tumors grow progressively in the host, it is not surprising that the majority of studies have focused on T lymphocytes that infiltrate these tumors. Although these studies have generated significant and useful information during the period of tumor

growth, they can only speculate on the mechanisms that are involved in tumor rejection. We have used a well developed sponge model of concomitant tumor immunity that allows us to compare the immunologic events that occur during tumor progression vs rejection. In this model, an animal harboring a primary EMT6 mammary tumor is challenged with a secondary tumor implant through a pre-implanted **gelatin** sponge. During the manifestation of concomitant tumor immunity, the secondary tumor is rejected and the effector cells mediating the response are retained within the sponge matrix. Using this model we analyzed the TCR usage, cytotoxic activity of lymphocytes, and cytokine production at both tumor sites. The data revealed that tumor-rejecting lymphocytes isolated from the site of secondary tumor implant were cytotoxic toward EMT6 cells, whereas tumor-infiltrating lymphocytes isolated from the progressing primary tumor were not. Interestingly, the TCR-V beta repertoire of the tumor-infiltrating lymphocytes and tumor-rejecting lymphocytes were identical with V beta 1 and V beta 8 being predominant at both sites. Furthermore, the rejection site showed higher gene expression of IFN-gamma, TNF-alpha, and IL-10 whereas **TGF-beta** expression was slightly higher in the progressing tumors. These findings suggest that the disparate effector functions observed during tumor progression vs rejection are not caused by different T cell phenotypes but may be due instead to influences exerted by cytokines produced at the tumor sites.

L32 ANSWER 11 OF 18 MEDLINE
95101831 Document Number: 95101831. Comparison of various delivery systems for **demineralized bone matrix** in a rat cranial defect model. Jazayeri M A; Nichter L S; Zhou Z Y; Wellisz T; Cheung D T. (Division of Plastic and Reconstructive Surgery, Childrens Hospital, Los Angeles, California.) JOURNAL OF CRANIOFACIAL SURGERY, (1994 Jul) 5 (3) 172-8; discussion 179. Journal code: A3J. ISSN: 1049-2275. Pub. country: United States. Language: English.

AB **Demineralized bone matrix** (DBM) has been successfully used as a substitute for bone grafting. Autogenous bone **grafts** may cause site morbidity and undergo significant resorption. DBM may overcome these problems, but it has no mechanical stability until bone formation has occurred. We tested various alloplastic implants (i.e., Surgicel, polydioxanone [PDS], porous polyethylene [Medpor], and Gelfoam) in combination with **DBM** and compared it with **DBM** alone in a 9 x 9 mm rat cranial defect model. Histological and biomechanical measurements were performed at postoperative month 2. Among the study groups, Gelfoam/**DBM** inhibited bone formation to varying degrees and was the only group that displayed an inflammatory response. Mechanical pushout tests using a servohydraulic testing frame were conducted. The Medpor/**DBM** implant displayed the strongest support at 2 months; maximum load was 95% of intact skull. Surgicel/**DBM** and **DBM** alone were comparable; maximum load was 66% of intact skull. Gelfoam/**DBM** and PDS/**DBM** displayed the weakest support (48% of intact skull). We conclude that, after 2 months of implantation, alloplastic/**DBM** composites provide osseous structural integration. Gelfoam/**DBM** is not an effective delivery system for **DBM** in our model.

L32 ANSWER 12 OF 18 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
92007028 EMBASE Document No.: 1992007028. Allogenic bone and cartilage morphogenesis. Rat BMP in vivo and in vitro. Kubler N.; Urist M.R.. Bone Research Laboratory, University of California, Rehabilitation Center, 1000

Veteran Avenue, Los Angeles, CA 90024, United States. Journal of Cranio-Maxillo-Facial Surgery 19/7 (283-288) 1991.
ISSN: 0301-0503. CODEN: JCMSET. Pub. Country: Germany. Language: English. Summary Language: English.

AB An allogenic aggregate of **bone morphogenetic protein** (BMP) and insoluble non-collagenous proteins (NCP) as well as a crude GuHCl extract were isolated from rats diaphyseal bones. Intramuscular implantation of 5 mg and 10 mg rat BMP/NCP in rats formed new ossicles, whereas 20 mg GuHCl extract failed to induce heterotopic bone formation. When 6 samples of inactivated rat bone matrix **gelatin** (BMG) were reconstituted with 0.75 mg of either BMP/NCP or GuHCl extract all 3 matrices reconstituted with BMP/NCP but only 1 out of 3 samples reconstituted with GuHCl extract induced heterotopic bone formation. Inactivated BMG alone did not show any osteoinductive activity.

The small amount of BMP/NCP necessary for osteoinduction when recombined with inactivated BMG suggests that growth factors in bone matrix without inherent bone-forming activity enhance BMP activity. In vitro, connective tissue outgrowths of neonatal rat muscle on a substratum of inactivated rat BMG differentiated into cartilage in response to 0.05 .mu.g/ml, 0.5 .mu.g/ml and 5.0 .mu.g/ml allogenic BMP/NCP added to the medium during the incubation period of 2 weeks. On day 14 of cultivation S35-sulphate incorporation into glycosaminoglycans (GAG) and H3-thymidine incorporation into DNA were measured, and the results related to the DNA content and the weight of the incubated muscle tissue, respectively. All doses of BMP/NCP increased GAG synthesis statistically significantly ($p < 0.05$ to $p < 0.001$). In contrast to that, DNA synthesis rate was not influenced by BMP/NCP. This suggests that GAG synthesis was not caused by cell proliferation but by cell differentiation.

L32 ANSWER 13 OF 18 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

91114201 EMBASE Document No.: 1991114201. Muscle tissue reactions to implantation of bone matrix **gelatin**. Okamoto Y.; Horisaka Y.; Matsumoto N.; Yoshimura Y.; Kawada J.; Yamashita K.; Takagi T.. Removable Prosthodontics Dept., School of Dentistry, Tokushima University, 3-18-15 Kuramoto,Tokushima 770, Japan. Clinical Orthopaedics and Related Research -/263 (242-253) 1991.
ISSN: 0009-921X. CODEN: CORTBR. Pub. Country: United States. Language: English. Summary Language: English.

AB Histologic changes of muscle tissue in the early stage of heterotopic osteogenesis induced by syngeneic insoluble bone matrix **gelatin** (BMG) with bone **morphogenetic protein** in rats was observed by light and electron microscopy. BMG induced cartilage in muscle tissue by Day 7 after its implantation, woven bone by Day 10, and lamellar bone with bone marrow by Day 14. The new findings in this work include (1) the disappearance of the basement membrane of muscle fibers; (2) the activation of the satellite cells of muscle fibers; (3) the appearance of fibroblastlike cells that closely resembled activated satellite cells among the degenerated muscle fibers or on the surface of the BMG; and (4) the change of fibroblastlike cells to chondroblasts or osteoblasts. These findings suggest that intramuscular implantation of BMG caused the conspicuous disappearance of the basement membrane of the muscle fiber and may play a part in osteogenesis induced by BMG.

L32 ANSWER 14 OF 18 MEDLINE DUPLICATE 5

90091176 Document Number: 90091176. Distal metaphyseal tibial nonunion. Deformity and bone loss treated by open reduction, internal fixation, and

human **bone morphogenetic protein** (hBMP).
Johnson E E; Urist M R; Finerman G A. (Division of Orthopaedic Surgery, University of California, Los Angeles 90024-1749.) CLINICAL ORTHOPAEDICS AND RELATED RESEARCH, (1990 Jan) (250) 234-40. Journal code: DFY. ISSN: 0009-921X. Pub. country: United States. Language: English.
AB Four patients with severely deformed nonunions of the distal end of the tibia failed to respond to standard surgical methods and were successfully treated as follows: debridement of fibrous tissue, sequestrectomy, correction of angulatory deformities, internal stabilization, and implantation of human **bone morphogenetic protein** (hBMP). After resection of the sequestra, all four patients had significant bone defects of the anterior tibial cortex extending to the ankle joint. The average number of failed previous surgical procedures was 5.8. The average patient age was 35.3 years. The intervals of nonunion averaged 24.8 months. In two patients, the hBMP, including other low molecular weight bone matrix noncollagenous proteins (hBMP/NCP), was implanted across the fracture site in polylactic-polyglycolic acid strips (1 X 13 cm) as an onlay **graft**. In one patient, the BMP was implanted in the fracture gap in absorbable **gelatin** (No. 5 capsules). In another patient, the BMP/NCP was also implanted in the form of a composite of cortical allogeneic bone in addition to a capsule of BMP/NCP. In all four cases, alignment was restored and the bone ends were stabilized with internal fixation. Preoperatively, the ankle joints were ankylosed and painful. Healed fractures and functional ankle joints were observed in three of four patients at an average of 4.4 months. In one patient, the fracture healed but the joint remained ankylosed. Although a randomized double-blind consecutive series of matched cases is necessary to prove the efficacy of hBMP, implants of hBMP combined with skillful surgical treatment are under investigation in the interim as an alternative to amputation.

L32 ANSWER 15 OF 18 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
90063579 EMBASE Document No.: 1990063579. Dog bone less osteogenetic than rat bone. Bone-matrix transplants in nude rats. Schwarz N.; Dinges H.P.; Schiesser A.; Redl H.; Schlag G.. Ludwig Boltzmann Institute for Experimental and Clinical Traumatology, Vienna, Austria. Acta Orthopaedica Scandinavica 60/6 (693-695) 1989.
ISSN: 0001-6470. CODEN: AOSAAK. Pub. Country: Denmark. Language: English. Summary Language: English.
AB **Demineralized bone matrix** and bone-matrix **gelatin** prepared from cortical rat bone, and from cortical and cancellous canine bone were implanted into muscle pouches of nude rats for 6 weeks. Evaluation was done by histology, histomorphometry, and determination of alkaline phosphatase. Rat matrix consistently induced new bone and high phosphatase levels. Canine matrix induced but small amounts of bone and lower phosphatase levels, with cortical matrix somewhat more inductive than cancellous matrix; demineralized cancellous bone matrix from the dog was the only material tested not showing any inductivity. Irrespective of bone type or species, **gelatin** had clearly higher induction capacity than **demineralized bone matrix**.

L32 ANSWER 16 OF 18 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
88054644 EMBASE Document No.: 1988054644. Bovine **bone morphogenetic protein** (bBMP) induced repair of skull

trephine defects in sheep. Lindholm T.C.; Lindholm T.S.; Alitalo I.; Urist
M.R.. Orthopaedic Hospital of the Invalid Foundation, SF-002 80 Helsingfors, Finland. Clinical Orthopaedics and Related Research -/227 (265-268) 1988.
ISSN: 0009-921X. CODEN: CORTBR. Pub. Country: United States. Language: English. Summary Language: English.
AB An aggregate of partially purified bovine **bone morphogenetic protein** (bBMP) and bone matrix insoluble noncollagenous proteins (iNCP), weighing a total of 100 mg of lyophilized BMP/iNCP, was implanted using ultra thin **gelatin** capsules in skull trephine defects in adult sheep. One hundred milligram samples of freeze-dried bovine serum albumin (BSA) were similarly implanted for controls. In five sheep, the capsules were implanted in 18-20 mm trephine skull defects and also in posterior cervical muscle pouches for heterotopic controls. In two out of five sheep, the trephines were repaired with bone as early as four weeks after the operation. Eight to 12
weeks after surgery repair was complete in the other three sheep. In the control contralateral trephines, one-third to one-half of the defect was incompletely repaired. Neither the BMP nor the BSA control implants induced bone formation in the muscle. While the BMP/iNCP prepared from bovine bone consistently induced regeneration in skull trephine defects, only fibrous tissue and no extraskeletal bone was induced to form in cervical muscle pouches in sheep.

L32 ANSWER 17 OF 18 MEDLINE DUPLICATE 6
88210960 Document Number: 88210960. **Bone morphogenetic protein** augmentation grafting of resistant femoral nonunions. A preliminary report. Johnson E E; Urist M R; Finerman G A. (Division of Orthopaedic Surgery, University of California, Los Angeles 90024.) CLINICAL ORTHOPAEDICS AND RELATED RESEARCH, (1988 May) (230) 257-65. Journal code: DFY. ISSN: 0009-921X. Pub. country: United States. Language:
English.
AB Twelve patients with intractable nonunions of the femoral diaphyseal or metaphyseal-diaphyseal shaft were successfully treated by a combination of
internal fixation and implants of human **bone morphogenetic protein** (h-BMP). There was an average of 4.3 surgical procedures per patient attempting union prior to h-BMP implantation. Union was obtained in 11 of 12 patients and in one patient with a repeat stabilization and implantation of h-BMP. Four patients received autogeneic cancellous bone **graft** and four patients received allogeneic bone **grafts**. The BMP implant was prepared in the form of an aggregate of h-BMP and bone matrix water-insoluble noncollagenous proteins (h-BMP/iNCP). Fifty to 100 mg of h-BMP/iNCP was either implanted in the fracture gap in ultra thin **gelatin** capsules, or incorporated in a strip of polylactic/polyglycolic acid copolymer (PLA/PGA) and placed as an onlay across the fracture gap. The average time to union was 4.7 months. Further clinical investigations are planned as a series of matched cases with and without BMP augmentation in order to distinguish h-BMP effects from new or improved methods of fracture fixation combined with autogeneic cancellous bone **grafts**
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L32 ANSWER 18 OF 18 MEDLINE DUPLICATE 7
87245172 Document Number: 87245172. Effect of bone marrow mononuclear phagocytes on the bone matrix-induced bone formation in rats. Sakata H; Takagi K. CLINICAL ORTHOPAEDICS AND RELATED RESEARCH, (1987 Jul) (220) 253-8. Journal code: DFY. ISSN: 0009-921X. Pub. country: United States.

Language: English.

AB Experimental ulnar bone defects in rats were grafted with freshly isolated whole bone marrow cells; bone marrow mononuclear phagocytes (macrophages); or both types of marrow cell preparations in combination with **demineralized bone matrix gelatin** (BMG). In the absence of BMG, the osteogenic performance of the marrow cell preparations was superior to that of the macrophages. In the presence of BMG (composite **grafts**), their osteogenic potential was nearly identical and significantly improved the level of bone formation stimulated by implants of BMG alone. The results encourage speculation and further research on sequential activities of bone marrow monocyte-macrophage (osteoclast) lineages and marrow stromal (osteoprogenitor) cell in **bone morphogenetic protein** (BMP)-induced regeneration.

L33 0 FILE MEDLINE
L34 2 FILE CAPLUS
L35 0 FILE BIOSIS
L36 0 FILE EMBASE
L37 2 FILE WPIDS

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L39 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2000 ACS DUPLICATE 1
1999:495201 Document No. 131:134686 Bone pastes comprising **osteogenic** compounds in a sterilized **gelatin** matrix.
Wironen, John F.; Felton, Phillip A.; Jaw, Rebecca (Regeneration Technologies, Inc., USA; University of Florida Tissue Bank, Inc.). PCT Int. Appl. WO 9938543 A2 19990805, 37 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US1677 19990127. PRIORITY: US 1998-14519 19980128; US 1998-154400 19980916.

AB A thermally sterilized bone paste useful in the orthopedic arts, for example in the repair of non-union fractures, periodontal ridge augmentation, craniofacial surgery, **implant** fixation, impaction grafting, or any other procedure in which generation of new bone is deemed necessary, is provided by a compn. comprising a substantially **bioabsorbable osteogenic** compd. in a matrix of 11-19 %, preferably 15-19 % of thermally sterilized **gelatin**. In various embodiments, the **osteogenic** compd. is selected from (1)

demineralized bone matrix (DBM); (2)
bioactive glass ceramic, Bioglass, bioactive ceramic, calcium phosphate ceramic, hydroxyapatite, hydroxyapatite carbonate, corraline hydroxyapatite, calcined bone, tricalcium phosphate, or like material; (3)
bone marrow exts., vascular proliferation or regeneration growth factors, **bone morphogenetic protein, TGF-beta.**, **PDGF**, or mixts. thereof, natural or recombinant; and (4) mixts. of (1)-(3). The thermally sterilized **gelatins** may be a com. available grade of **gelatins** which is both thermally and irradiatively sterilized.

L39 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2000 ACS DUPLICATE 2
1998:624020 Document No. 129:250241 Bone paste comprising a **bioabsorbable osteogenic** compound in a **gelatin** matrix. Wironen, John F.; Grooms, Jamie M. (University of Florida Tissue Bank, Inc., USA; University of Florida Research Foundation, Inc.). PCT Int. Appl. WO 9840113 A1 19980917, 39 pp. DESIGNATED STATES: W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US4904 19980312. PRIORITY: US 1997-816079 19970313.
AB A bone paste useful in the orthopedic arts, for example in the repair of non-union fractures, periodontal ridge augmentation, craniofacial surgery, **implant** fixation, impaction grafting, or any other procedure in which generation of new bone is deemed necessary, is provided by a compn. comprising a substantially **bioabsorbable osteogenic** compd. in a **gelatin** matrix. In various embodiments, the **osteogenic** compd. is selected from (1) **demineralized bone matrix** (DBM); (2) bioactive glass ceramic, Bioglass, bioactive ceramic, calcium phosphate ceramic, hydroxyapatite, hydroxyapatite carbonate, corraline hydroxyapatite, calcined bone, tricalcium phosphate, or like material; (3) **bone morphogenetic protein, TGF-beta.**, **PDGF**, or mixts. thereof, natural or recombinant; and (4) mixts. of (1)-(3). The bone paste contains dry demineralized bone 0-40, lyophilized thermally crosslinkable **gelatin** 20-45, Bioglass 0-40%, and bone morphogenic protein 0.001 mg/mL. The bone paste was osteoinductive when **implanted** in rats.

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L14 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1996:455578 CAPLUS
DOCUMENT NUMBER: 125:151095
TITLE: Comparative histological study of mineralizations after intramuscular **implantations** of heat-denatured demineralized **bone matrix gelatin, heat**-denatured demineralized tooth, and cross-linked collagen
AUTHOR(S): Ninomiya, Masami
CORPORATE SOURCE: Sch. Dent., Univ. Tokushima, Tokushima, 770, Japan
SOURCE: Shikoku Shigakkai Zasshi (**1996**), 9(1), 77-97
CODEN: SSZAED; ISSN: 0914-6091
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

AB I.m. **implantation** of demineralized **bone matrix gelatin** (BMG) is known to form spherical mineralized deposits in the **implant** prior to **bone** tissue formation induced by **bone** morphogenetic protein (BMP). This type of mineralization is called "acellular mineral deposition (AMD)", which is not assocd. with osteogenic cells. In the present study, heat-denatured BMG, heat-denatured demineralized tooth, and calf skin type I collagen cross-linked with glutaraldehyde were resp. **implanted** into the rectus abdominis muscles in rats. Then mineralized deposits formed in the **implants** after the resp. **implantations** were compared by means of histol. anal.by using light and electron microscopes. Compns. of these deposits were also analyzed by electron probe x-ray microanal. Heat-denatured BMG, which was prepd. at 150.degree. for 30 min to inactivate non-collagenous proteins including BMP (NCP), was used to investigate whether NCP had some roles in AMD process. Heat-denatured demineralized tooth and crosslinked collagen were also used to examine the relations of AMD with calcification of dentin and with matrix collagen. In heat-denatured BMG, spherical mineralized deposits initially appeared at day 3 and then gradually increased in the size and the no. Finally these deposits fused with each other to occupy the whole **implant** at day 14. Similar observations were obtained in the case of heat-denatured demineralized tooth **implant**. Mineralization was progressed in one way from enamel side to dental pulp side. Predentin area did not easily mineralized during the exptl. period. In crosslinked collagen, fiber-like mineralized deposits were scattered along collagen fiber bundles at day 3. These deposits gradually increased in the no. and invaded into the surrounding collagen fibers to increase in the size, and then these deposits fused with each other to occupy the whole **implant** at day 14. **Bone** and cartilaginous tissues did not appear around the **implants**, and also there were no osteoblast- and osteoclast-like cells in any **implants**. Mineralized deposits were formed compactly showing needle-shaped crystals in all **implants**. Compn. anal. revealed that these deposits showed a similar mol. ratio of calcium to phosphorus. AMD occurs with no relation to the subsequent **bone** tissue formation and that NCP never have any roles in AMD process. AMD physicochem. occurs depending on cross-linked collagen of matrix and that AMD obsd. in the **implanted** dentin may take place in the physiol. mineralization because of the morphol. similarity between AMD and globular dentin.

TI Comparative histological study of mineralizations after intramuscular

implantations of heat-denatured demineralized **bone matrix gelatin**, **heat**-denatured demineralized tooth, and cross-linked collagen

SO Shikoku Shigakkai Zasshi (**1996**), 9(1), 77-97
CODEN: SSZAED; ISSN: 0914-6091

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ST histol mineralization **implant bone** gelatin; tooth histol mineralization **bone**; collagen histol mineralization **implant**

IT **Bone**
Tooth
(histol. study of mineralizations after i.m. **implantations** of **bone matrix gelatin** and and collagen)

IT Gelatins, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(histol. study of mineralizations after i.m. **implantations** of **bone matrix gelatin** and and collagen)

IT Dental materials and appliances
Prosthetic materials and Prosthetics
(**implants**, histol. study of mineralizations after i.m. **implantations** of **bone matrix gelatin** and and collagen)

IT Collagens, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(reaction products, histol. study of mineralizations after i.m. **implantations** of **bone matrix gelatin** and and collagen)